Inherited immunodeficiency diseases.

Immunodeficiencies occur when one or more components of the immune system is defective. The commonest cause of immune deficiency worldwide is malnutrition; however, in developed countries, most immunodeficiency diseases are inherited, and these are usually seen in the clinic as recurrent or overwhelming infections in very young children. Less commonly acquired immunodeficiencies with causes other than malnutrition can manifest later in life. While the pathogenesis of many of these acquired disorders has remained obscure, some are caused by known agents, such as drugs or irradiation which damage lymphocytes, or infection with HIV. By examining which infections accompany a particular inherited or acquired immunodeficiency, we can see which components of the immune system are important in the response to particular infectious agents. The inherited immunodeficiency diseases also reveal how interactions between different cell types contribute to the immune response and to the developmental sequence of T and B lymphocytes. Finally, these diseases can lead us to the defective gene, often revealing new information about the molecular basis of immune processes and providing the necessary information for diagnosis, genetic counseling, and gene therapy.

10-6 Inherited immunodeficiency diseases are caused by recessive gene defects.

Before the advent of antibiotic therapy, it is likely that most individuals with inherited immune defects died in infancy or early childhood because of their susceptibility to particular classes of pathogens (Fig. 10.8). Such deaths would not have been easy to identify, since many normal infants also died of infection. Thus, the first immunodeficiency disease was not described until 1952; since that time many inherited immunodeficiency diseases have been identified. Most of the gene defects that cause these inherited immunodeficiencies are recessive, and for this reason, many common immunodeficiencies are caused by mutations of genes on the X chromosome. Recessive defects cause disease only when both chromosomes are defective. As males have only one X chromosome, however, all males who inherit an X chromosome carrying a defective gene will manifest disease, whereas female carriers, having two X chromosomes, are perfectly healthy. Immunodeficiency diseases that affect many steps in B- and T-lymphocyte development have been described, as have defects in surface molecules that are important for T- or B-cell function. Defects in phagocytic cells, in complement, in cytokines, in cytokine receptors, and in molecules that mediate effector responses also occur (see Fig. 10.8). Thus immunodeficiency may be caused by defects either in the adaptive or the innate immune system. Individual examples of these diseases will be described in later sections.

More recently, the use of gene knock-out techniques in mice has allowed the creation of many immunodeficient states that are adding rapidly to our knowledge of the contribution of individual molecules to normal immune function. Nevertheless, human immunodeficiency disease is still the best source of insight into host defense in humans. The study of immunodeficiency provides the clearest evidence of the normal pathways of host defense against infectious disease. For example, as we will see later, deficiency in antibody, complement, or phagocytic function

Fig. 10.8 Human immunodeficiency syndromes. The specific gene defect, the consequence for the immune system, and the resulting disease susceptibilities are listed for some common and some rare human immunodeficiency syndromes. ADA, adenosine deaminase; PNP, purine nucleotide phosphorylase; TAP, transporters associated with antigen processing; WASP, Wiskott-Aldrich syndrome protein; EBV, Epstein-Barr virus; NK, natural killer.

Name of deficiency syndrome	Specific abnormality	Immune defect	Susceptibility
Severe combined immune deficiency	ADA deficiency	No T or B cells	General
	PNP deficiency	No T or B cells	General
	X-linked self γ chain deficiency	No T cells	General
	Autosomal self DNA repair defect	No T or B cells	General
DiGeorge syndrome	Thymic aplasia	Variable numbers of T and B cells	General
MHC class I deficiency	TAP mutations	No CD8 T cells	Viruses
MHC class II deficiency	Lack of expression of MHC class II	No CD4 T cells	General
Wiskott-Aldrich syndrome	X-linked defective WASP gene	Defective polysaccharide antibody responses	Encapsulated extracellular bacteria
Common variable immunodeficiency	Unknown, MHC-linked	Defective antibody production	Extracellular bacteria
X-linked agammaglobulinemia	Loss of Btk tyrosine kinase	No B cells	Extracellular bacteria, viruses
X-linked hyper-IgM syndrome	Defective CD40 ligand	No isotype switching	Extracellular bacteria
Selective IgA and/or IgG deficiency	Unknown, MHC-linked	No IgA synthesis	Respiratory infections
Phagocyte deficiencies	Many different	Loss of phagocyte function	Extracellular bacteria
Complement deficiencies	Many different	Loss of specific complement components	Extracellular bacteria especially *Neisseria* spp.
Natural killer (NK) cell defect	Unknown	Loss of NK function	Herpes viruses
X-linked lymphoproliferative syndrome	Unknown, X-linked	EBV-triggered immunodeficiency	EBV
Ataxia telangiectasia	Gene with PI-3 kinase homology	T cells reduced	Respiratory infections
Autoimmune lymphoproliferative disease	Mutant Fas	Failure of T- and B-cell apoptosis	Autoimmune disorders

each increases the risk of infection by certain pyogenic bacteria. This shows that the normal pathway of host defense against such bacteria is binding of antibody followed by fixation of complement, which allows uptake of opsonized bacteria by phagocytic cells. Breaking any one of the links in this chain of events leading to bacterial killing causes a similar immunodeficient state.

The study of immunodeficiency also teaches us about the redundancy of mechanisms of host defense against infectious disease. The first two humans to be discovered with hereditary deficiency of complement were healthy immunologists. This teaches us two lessons. The first is that there are multiple protective immune mechanisms against infection; for example, while there is abundant evidence that complement deficiency increases susceptibility to pyogenic infection, not every human with complement deficiency suffers from recurrent infections. The second lesson is about the phenomenon of **ascertainment artefact**. When an unusual observation is made in a patient with disease, there is a temptation to seek a causal link. However, no one would suggest that complement deficiency causes a genetic predisposition to becoming an immunologist. Complement deficiency was discovered in immunologists because they used their own blood in their experiments. If a particular measurement is only made in a group of patients with a particular disease, it is inevitable that the only abnormal results will be discovered in patients with that disease. This is an ascertainment artefact and emphasizes the importance of studying appropriate controls.

10-7 The main effect of low levels of antibody is an inability to clear extracellular bacteria.

Pyogenic or pus-forming bacteria have polysaccharide capsules which make them resistant to phagocytosis. Normal individuals can clear infections by such bacteria because antibody and complement opsonize the bacteria, making it possible for phagocytes to ingest and destroy them. The principal effect of deficiencies in antibody production is therefore failure to control this class of bacterial infection, although susceptibility to some viral infections, most notably those caused by enteroviruses, is also increased because of the importance of antibodies in neutralizing infectious viruses that enter the body through the gut (see Chapter 8).

The first description of an immunodeficiency disease was Ogden C. Bruton's account, in 1952, of the failure of a male child to produce antibody. As this defect is inherited in an X-linked fashion and is characterized by the absence of immunoglobulin in the serum, it was called **Bruton's X-linked agammaglobulinemia (XLA)**. The absence of antibody can be detected using electrophoresis (see Section 2-9). Since then, many more diseases of antibody production have been described, most of them the consequence of failures in the development or activation of B lymphocytes.

The defective gene in XLA is now known to encode a protein tyrosine kinase known as Btk (Bruton's tyrosine kinase). This protein is expressed in polymorphonuclear neutrophilic leukocytes as well as in B cells, although only B cells are defective in these patients, in whom B-cell maturation halts at the pre-B-cell stage. Thus it is likely that Btk is required to couple the pre-B-cell receptor (which consists of heavy chains, surrogate light chains, and Igα and Igβ) to nuclear events that lead to pre-B-cell growth and differentiation. A homologous kinase called Itk has been found in T cells and is required for normal T-cell development. Defects in Btk are analogous to defects in Lck in T-cell development (see Section 6-8). In the mouse, Lck deficiency leads to the arrest of thymocyte development at the double-negative stage, after T-cell receptor β-chain gene rearrangement and cell-surface expression but before the rearrangement of the α-chain genes. Thus, there may be a cascade of tyrosine kinases, involving Lck and Itk in double-negative thymocytes, and Blk and Btk in pre-B cells, that is important for lymphocyte development. In both Lck and Btk deficiencies,

some B or T cells mature despite the defect in the signaling molecule, suggesting that signals transmitted by these kinases promote rearrangement of light-chain or α chain genes, respectively, but are not absolutely required.

Since the gene responsible for XLA is found on the X chromosome, it is possible to identify female carriers by analyzing X-chromosome inactivation in their B cells. During development, female cells randomly inactivate one of their two X chromosomes. Since the product of a normal *btk* gene is required for normal B-lymphocyte development, only cells in which the X chromosome carrying the normal allele of *btk* is active can develop into mature B cells (with a very few exceptions, see earlier). Thus, in female carriers of mutant *btk* genes, almost all B cells have the normal X chromosome as the active X. By contrast, the active X chromosomes in the T cells and macrophages of carriers are equally distributed between normal and *btk* mutants. This fact allowed female carriers of XLA to be identified even before the nature of *btk* was known. Non-random X inactivation only in B cells also demonstrates conclusively that the *btk* gene is required for normal B-cell development but not for the development of other cell types, and that Btk must act within B cells rather than on stromal cells or other cells required for B-cell development (Fig. 10.9c).

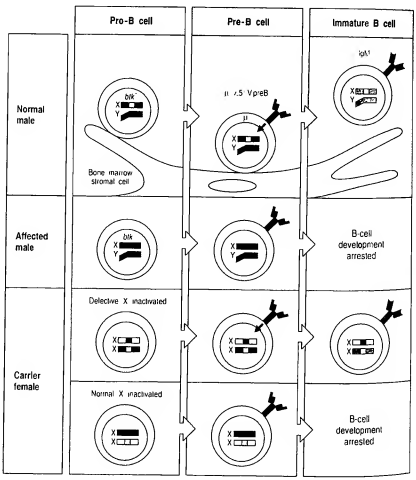

Fig. 10.9 The product of the *btk* gene is important for B-cell development. In X-linked agammaglobulinemia (XLA), a protein tyrosine kinase called Btk, encoded on the X chromosome, is defective. In normal individuals, B-cell development proceeds through a stage in which the pre-B cell receptor consisting of μ:λ5:Vpre-B transduces a signal via Btk, triggering further B-cell development. In males with XLA, no signal can be transduced and although the pre-B-cell receptor is expressed, the B cells develop no further. In female mammals, including humans, one of the two X chromosomes in each cell is permanently inactivated early in development. Since the choice of which chromosome to inactivate is random, half of the pre-B cells in a carrier female express a wild-type *btk*, while half express the defective gene. None of the B cells that express *btk* from the defective chromosome can develop into mature B cells. Therefore, in the carrier, mature B cells always have the non-defective X chromosome active. This is in sharp contrast to all other cell types, which express the non-defective chromosome in only half of the population. Non-random X chromosome inactivation in a particular cell lineage is a clear indication that the product of the X-linked gene is required for the development of cells of that lineage. It is also sometimes possible to identify the stage at which the gene product is required, by detecting the point in development at which X-chromosome inactivation develops bias. Using this kind of analysis, one can identify carriers of X-linked traits such as XLA without needing to know the nature of the mutant gene.

IMMUNOBIOLOGY

THE IMMUNE SYSTEM IN HEALTH AND DISEASE

THIRD EDITION

Charles A. Janeway, Jr.
Yale University Medical School

■

Paul Travers
Birkbeck College, London University

with the assistance of

Simon Hunt
Oxford University

■

Mark Walport
Royal Postgraduate Medical School, London

CB
CURRENT
BIOLOGY
LIMITED ■

Current Biology Ltd
London, San Francisco and New York

GP

Garland Publishing Inc
New York and London

Text editors: Penelope Austin, Eleanor Lawrence, Miranda Robertson
Project editors: Emma Hunt, Giles Montier, Hazel Richardson
Illustrators: Celia Welcomme, Matthew McClements
Layout: Huw Woodman
Production: Kate Oldfield, Priya Gohil
Software support: Gary Brown
Proofreader: Melanie Paton
Indexer: Liza Weinkove

Distributors
Inside North America: Garland Publishing Inc., 717 Fifth Avenue, New York, NY 10022, USA.
Inside Japan: Nankodo Co. Ltd., 42-6, Hongo 3-Chome, Bunkyo-ku, Tokyo 113, Japan.
Outside North America and Japan: Churchill Livingstone, Robert Stevenson House, 1-3 Baxter's Place, Leith Walk, Edinburgh, EH1 3AF.

ISBN 0-8153-2818-4 (paperback) Garland
ISBN 0-443-05964-0 (paperback) Churchill Livingstone
ISBN 0-443-05995-0 (paperback) International Edition

A catalog record for this book is available from the British Library.

Library of Congress Cataloging-in-Publication Data
Janeway, Charles.
Immunobiology: the immune system in health and disease/ Charles A. Janeway, Jr., Paul Travers.—Third ed.
p. cm.
Includes bibliographical references and Index.
ISBN 0-8153-2818-4 (pbk.).
1. Immunity. I. Travers, Paul, 1956- .
II. Title
QR181.J37 1997
616. 07'9—dc21

96-47915
CIP

This book was produced using Corel Ventura Publisher 5.0 and CorelDRAW 5.0.

Printed in Singapore by Stamford Press.

Published by Current Biology Ltd., Middlesex House, 34-42 Cleveland Street, London W1P 6LB, UK and Garland Publishing Inc., 717 Fifth Avenue, New York, NY 10022, USA.